REMARKS

Claims 1-38 are pending in the above-identified application. Claims 28, 29, 37 and 38 have been cancelled without prejudice as being drawn to a non-elected invention. Applicant reserves the right to pursue these withdrawn claims in a later filed application claiming the benefit of priority to the above-identified application. Upon entry of the amendments, claims 1-27 and 30-36 will be pending and under examination.

Rejections Under 35 U.S.C. §112, First Paragraph

Claim 1-27 and 30-36 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement allegedly because it would be unpredictable to practice the invention as claimed. In this regard, the office action asserts that undue experimentation is required because no phenotype is described nor are there working examples provided for the transgenic mice. The office action also asserts that undue experimentation would be required to practice the invention as claimed allegedly because of the unpredictable nature of homologous recombination. Ryan et al. is cited as providing support for this assertion. Also cited is Lem et al. to support the assertion that rhodopsin knockout mice may result in photoreceptor cell degeneration. Further, Holschneider et al. is cited in the office action as allegedly support for the assertion that transgenic expression varies with particular gene constructs.

The claims are directed to a gene targeting construct or vector encoding a transgene having a rod outer segment (ROS) targeting signal flanked by homologous sequences to the mouse rhodopsin gene and to a mouse cell or mouse whose genome is functionally disrupted at one or both endogenous rhodopsin gene alleles with the targeting construct. The application provides sufficient teachings and guidance for the claimed gene targeting construct, mouse cell and mouse to allow those skilled in the art to practice the invention as claimed. As described further below, the rationales provided in the office action are inapplicable to making and using the invention as claimed.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Genentech, Inc. v. Novo Nodisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997), *see also* MPEP §2164.01(c), fourth paragraph. Further, in *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998), the Federal Circuit clearly stated that routine experimentation does not constitute undue experimentation:

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Id. (*citing PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996); *see also In re Wands*, 858 F.2d 731, 736-40 (Fed. Cir. 1988)).

Predictability of the claimed invention is not prefaced on obtaining a phenotype for a mouse cell or mouse harboring a gene construct of the claimed invention. The application provides sufficient teachings and guidance to make and use the claimed gene constructs without undue experimentation and with a reasonable amount of predictability. While not conceding, as asserted in the office action, that the only use for the construct, vector and mouse cell described in the specification is for making a transgenic mouse having a functional rhodopsin gene disruption which expresses a polypeptide of interest, the application nevertheless enables this use without undue experimentation.

The application teaches methods well know in the art for making and using the invention as claimed. The methods for generating the transgene containing constructs and for introducing them into a cell or mouse genome is well known in the art. Any experimentation required to practice the invention as claimed can be considered routine. For example, the application teaches at page 6, lines 5-8, that a transgene can encode any polypeptide for which an encoding

sequence is known or can be determined. At page 6, line 3 through page 10, line 3, the application further teaches numerous examples of transgenes that can be employed in the methods of the invention. Page 10, lines 12-25, the application teaches the attachment of membrane localization signal, including a rod outer segment (ROS) targeting signal for localization of a transgene encoded polypeptide a membrane including a ROS membrane. Page 18, line 23 through page 21, line 10, for example, describe numerous ROS sequences and method of implementation that can be used in the gene constructs of the invention.

The application further teaches, for example, at page 13, line 12, through page 15, line 22, that the transgene is flanked by 5' and 3' DNA sequences homologous to a rhodopsin gene for gene targeting. The degree of identity and size of flanking sequences useful in the claimed constructs of the invention is also described. The application also describes that operable association of a transgene and rod-specific regulatory sequences at, for example, page 15, line 23 through page 16, line 2, and provides numerous examples at pages 15-18.

Further, the application teaches exemplary methods for confirming that the constructs and vectors direct rod-specific gene expression. For example, at page 18, line 10-22, the application describes a convenient assay for confirming rod-specific gene expression from a particular regulatory sequence. The assay entails the use of a detectable reporter gene linked to the construct and transfection into *Xenopus* embryos. Detection of the reporter transgene in resultant tadpoles demonstrates operability of the construct. The application teaches, for example, at page 18, lines 16-22, that the methods used for such confirmation are well known in the art.

The application also teaches an exemplary method for confirming the function of a ROS targeting signal at, for example, page 21, lines 11-20. The procedure involves methods well known in the art such as transgenically expressing a transgene encoding polypeptide/ROS fusion in *Xenopus* and observing localization to rod outer segments by microscopy. Transgenic expression and confirmation by microscopy was well known in the art as described by Moritz et al. and Tam et al., cited at page 21, lines 19-20, of the application. Page 21, lines 21-28, describe the use of this method with transgenic *Xenopus* expressing a human cannabinoid receptor 2

(CB2) and immunolocalization with a CB2 antibody. The application further teaches, for example, at page 22, line 1 through page 24, line 9, the use of positive and negative selection markers sequence configurations well known in the art for inserting and selecting homologous recombinants.

The application additionally provides sufficient teachings at, for example, page 26, line 26 through page 32, line 21, for how to make and use a cell or animal whose genome contains a functional disruption of one or both endogenous rhodopsin alleles and also contains a transgene encoding a polypeptide consisting of an ROS targeting signal operably associated with a rod-specific regulatory sequence. In this regard, page 28, lines 6-19, describe, for example, the functional disruption of rhodopsin by gene knock-in and beginning at page 29, line 7, the application describes more than seven alternative methods well known in the art for introducing the gene targeting constructs into cells. Further, at page 30, line 7 through page 32, line 21, the application provides numerous teachings and guidance for generating knock-in animals with cells having the transgene inserted into its genome by homologous recombination. As described therein and exemplified by numerous citation, these methods were all well known in the art at the time the application was filed.

For example, the application teaches the use of embryonic stem (ES) cells introduced into blastocysts as well as the introduction of a transgene construct into the male pronucleus of a fertilized egg and implantation into a pseudopregnant female (page 31, line 17 through page 32, line 2). Further, the application teaches at least three alternative methods well known to those skilled in the art at, for example, page 32, lines 3-13, for introducing transgenes into animals. Such methods include retrovirus mediated gene transfer, electroporation of embryos and sperm-mediated gene transfer.

As described above and taught throughout the application, once the cells are made having an inserted transgene that is targeted to the ROS, it is routine to generate the animals that similarly express the transgene in ROS. As described above, the methods for confirming expression and localization are well known in the art. Following generation of an animal

expressing the transgene, the expressed polypeptide can be isolated and used in a variety of procedures. Methods for isolation from rod cells are similarly well known in the art and also are taught in the application at, for example, page 32, line 22 through page 34, line 29. Further, the application provides numerous examples of the claimed constructs, vectors, mouse cells and mouse as well as exemplifies their construction and use in Examples I-III (pages 39-42).

In light of these teachings and guidance in the specification, undue experimentation is not required to practice the invention as claimed because experimentation, if any, is routine due to use of methods well known in the art; there is sufficient direction and guidance for making and using the invention as claimed; numerous examples are provided in the application; homologous recombination and transgenic technology is well known; the skill level of those in the art is high due to the use of recombinant and transgenic technology and there is reasonable predictability in the outcome because known methods are available for confirmation.

Each publication cited in the office action allegedly supporting the assertion that undue experimentation is required is inapplicable to the teachings and guidance provided in the application for how to make and use the invention as claimed.

Ryan et al. is inapplicable because the invention directed to a gene construct or vector, or to a mouse cell or mouse whose endogenous rhodopsin gene is functionally disrupted by the construct. There is no claimed requirement for a phenotype in any of these claims. Nor does the use of the claimed construct, vector, cell or mouse require a phenotype. Initially, the Examiner's attention is drawn to the fact that gene constructs or vectors do not exhibit phenotypes. Further, the claimed cells and mouse, although capable of exhibiting phenotypes, are not claimed as such nor do they require a phenotype for their use. Instead, these claims recite that the host genome have a functional disruption of one or both endogenous rhodopsin alleles. As taught in the application at, for example, page 18, lines 10-22 and at page 21, lines 11-28, the functional disruption and targeted expression can be determined by methods such as measuring polypeptide expression or immunolocalization. Therefore, determination of a phenotype is not required to practice the invention as claimed.

Manifestation of a phenotype also is not required to practice the invention as claimed without undue experimentation because one purpose of the invention is polypeptide production of the transgene encoded product for subsequent isolation and use. Expression of a polypeptide product in isolatable quantities from a host cell or animal is routine. Failure to correlate a phenotype with the expressed product is inapplicable to practicing the invention as claimed. Instead, determination of the expression and production of isolatable quantities of an encoded transgene product can be accomplished by making the cells or animal and measuring whether the transgene product is produced. As described previously, the application provides sufficient teachings and guidance for making and confirming the expression of a transgene product inserted by homologous recombination. Accordingly, the application sufficiently teaches how to make and use the invention as claimed without undue experimentation irrespective of an associated phenotype.

Lem et al., cited as support for the assertion that rhodopsin knockout mice may result in photoreceptor cell degeneration, is inapplicable to the claimed invention. For example, the office action cites the abstract from Lim et al. which states that "[r]etinas in mice lacking both opsin alleles <u>initially developed normally</u>" (emphasis added). Lim et al. describes, for example, at page 739, column 2, that retinal degeneration was initially observed by 90 days after birth. While not conceding that Lim et al. teaches the degeneration of all rod cells at 1.5 months post-birth, even if such rod cells expressing a transgene always did degenerate, rod cells are sufficiently developed prior to this time to achieve ample protein expression capacity. Therefore, the observation that cells may degenerate under certain conditions does not preclude the fact there is a window of at least 1.5 months after birth where transgene expression can occur to produce the encoded product of interest. Accordingly, the Lim et al. fails to support a conclusion of undue experimentation to practice the invention as claimed.

Similarly, Holschneider et al. also is inapplicable to the claimed invention. As described above, the application provides sufficient teachings and guidance to practice the invention as claimed without undue experimentation because, for example, the methods that can be employed

to make and use the invention are well known in the art, homologous recombination and transgenic technology is well known and known methods are available for confirmation.

Holschneider et al. does not support lack of enablement as asserted in the office action because the application teaches the construction of a transgene encoding polypeptide having a ROS target signal flanked by sequences for homologous recombination and operable association with a rod-specific regulatory signal. Therefore, the construct, vector, cell and mouse of the invention claim a transgene under sufficient control that variability in expression is minimized. Moreover, the application teaches convenient methods to confirm transgene expression and targeting after homologous recombination, again minimizing or avoiding variability in expression of the transgene product. Further, Holschneider et al. is concerned with observing changes in phenotype. As described previously, use of the invention as claimed is independent of any change in phenotype or lack of a phenotypic change. Instead, any use based on expression of the transgene can be routinely practiced by making the claimed construct, vector, cell or mouse and determining whether it expresses the transgene product as taught in the application. Accordingly, Holschneider et al. fails to provide an adequate basis for lack of predictability of the claimed invention.

In light of the above remarks, Applicants maintain that the application sufficiently teaches how enables the invention as claimed. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

CONCLUSION

In light of the remarks herein, Applicants submit that the claims are in condition for allowance and respectfully requests a notice to this effect. Should the Examiner have any questions related to this application, she is invited to contact the undersigned attorney.

Respectfully submitted,

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